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Contemporary Review

The modernized classification of cardiac antiarrhythmic drugs: Its application to clinical practice

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ABSTRACT

Cardiac arrhythmias pose a major public health problem, and pharmacologic intervention remains key to their therapy. The 1970 landmark Vaughan Williams (VW) classification utilizing known actions of then available antiarrhythmic drugs (AADs) became and remains central to management, but it requires revision in response to extensive subsequent advances. Our modernized AAD classification reflected and sought to facilitate such fundamental physiological and clinical development. Here we respond to requests for an adaptation of our scheme specifically focused on clinical practice. (1) This adaptation improves the accessibility of our original scheme to clinical practice, focusing on key AADs in clinical use rather than investigational new drugs (INDs) while conserving and encompassing the classic VW scheme. (2) We preserve a rational conceptual framework based on current understanding of the relevant electrophysiological events, their underlying cellular or molecular cardiomyocyte targets, and the functional mechanisms they mediate. (3) The adopted subclasses within each AAD class parallel clinical practice by including only subclasses containing established AADs, or approved potential off-label drugs, as opposed to those only including INDs. (4) The simplified scheme remains flexible, permitting drugs to be placed in multiple classes where required, and the addition of classes and subclasses in light of future investigations and clinical approvals. Thus, we derive from our comprehensive modernized AAD classification a more focused and simpler scheme for clinical use. This both modernizes yet preserves the classic VW classification and remains flexible, thus accommodating future developments.

KEYWORDS Miles Vaughan Williams; Antiarrhythmic drugs; Cardiac arrhythmias; Ion channels; Ca^{2+} homeostasis

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Antiarrhythmic drug classification in clinical practice

Cardiac arrhythmias pose a major public health problem, and pharmacologic intervention remains the mainstay of antiarrhythmic therapy. Miles Vaughan Williams (VW) first proposed a landmark classification of cardiac antiarrhythmic drugs (AADs) based on their then-established electrophysiological and pharmacologic actions on cardiac action potential (AP) components and their relationship to arrhythmias.[1,2] Its effectiveness resulted in the VW approach becoming and remaining to the present time central to clinical management. However, subsequent substantial progress in new therapeutic agents created requirements for revised classification schemes. In response to this, in 2018 we introduced a modernized classification of AADs in order to facilitate both clinical practice and drug discovery (Figure 1A).[3] Given the desirability of enhancing its clinical usefulness, here we simplify the modernized scheme to a form specifically focused on clinical practice. We nevertheless have continued to utilize its organization of drug classes and subclasses, and we include some updates on subsequent progress in AAD development.

A more focused AAD classification

First, a simplified classification should improve the accessibility of our scheme to clinical practice. We now focus on key drugs in clinical rather than investigational use. We emphasize that the drug classes in both this current 2025 version and the initial 2018 version (Figure 1A) utilized, and encompassed drugs and drug targets within, the VW scheme (Figure 1A[b]), extended

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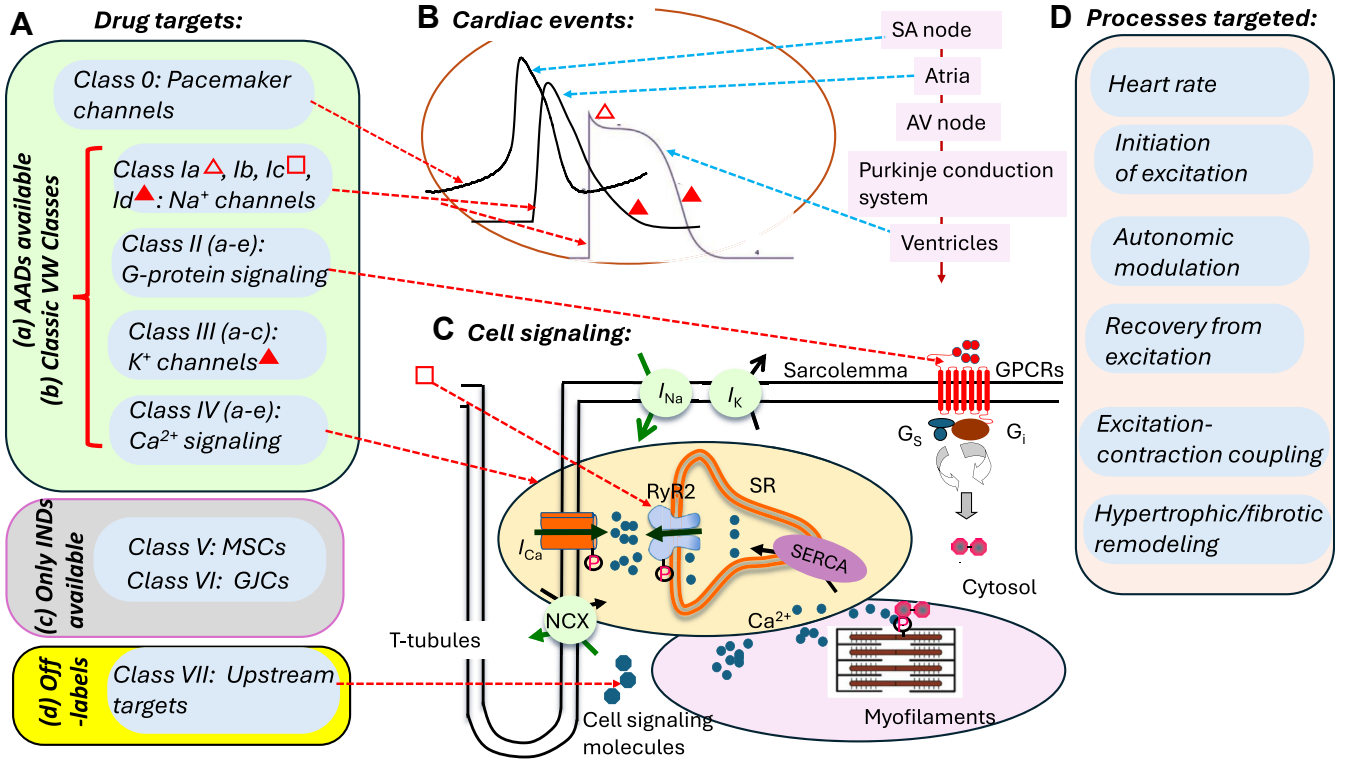

Figure 1
The 2018 modernized classification scheme for anti-arrhythmic drugs (AADs) with its new or revised classes and subclasses. **A:** Its clinical adaptation in terms of established AADs (**a**), including drugs classifiable within the Vaughan Williams scheme (**b**), investigational new drugs (IND) comprising mechanosensitive (MSC) and gap junction channels (GJC) (**c**) and potential off label drugs for upstream targets (**d**). **B-D:** Correlations of the classification scheme with: (**B**) electrophysiological events reflecting sino-atrial node (SAN), atrial, Purkinje conducting and ventricular APs producing a propagated wave of electrical activity through their respective cardiomyocytes. **C:** biomolecular targets including ionic currents, intracellular signaling, and autonomic modulatory events. These mediate (**D**) the underlying component physiological processes underlying cardiomyocyte activation. The latter involve surface membrane Na^+, K^+ and Ca^{2+} currents (I_{Na}, I_K, I_{Ca},) and Na^+/Ca^{2+} exchange (NCX) activity. Further signaling events include G_i and G_s, G-protein signaling following G-protein coupled receptor (GPCRs) activation, intracellular SR membrane, cardiac ryanodine receptor, type 2 (RyR2) mediated Ca^{2+} release and Ca^{2+} transport (SERCA)-mediated SR Ca^{2+} re-uptake. Red dotted arrows link drug classes (**A**) to corresponding action potential (AP) phases (**B**). Blue dotted arrows link specific cardiac conducting regions to their associated AP waveforms (**B**). Open triangles link inhibitory actions on I_{to} of Class Ia drugs, exemplified by quinidine (**A**), on early Phase 1 AP repolarization (**B**). Filled triangles link inhibitory actions on I_{NaL} and I_K of Class Id (exemplified by ranolazine) and Class III drugs respectively (**A**) with contrasting repolarization actions on AP duration (**B**). Squares link RyR2 effects shown by Class Ic (exemplified by flecainide) (**A**) with actions on Ca^{2+} homeostasis (**C**).

to include subsequently approved antiarrhythmic drugs (AADs) (Figures 1A[a] and 1A[b]), potential off-label drugs (Figure 1A[d]), and investigational new drugs (INDs) (Figure 1A[c]). Thus, the retained Class I contains drugs producing moderate (Ia), weak (Ib), or marked (Ic) Na^+ channel ($Na_v1.5$) block. They reduce AP phase 0 slope and overshoot, while respectively increasing, reducing, or conserving AP durations and effective refractory periods (ERPs).[4] This was extended to include particular delayed Na^+ current (I_{NaL}) components. Class II, originally grouping β-adrenergic inhibitors reducing sinoatrial node (SAN) pacing rates and slowing atrioventricular node (AVN) AP conduction,[4,5] was extended by incorporating the extensive advances in our understanding of autonomic, often G-protein–mediated, signaling. Extension of Class III comprising K^+ channel blockers delaying AP phase 3 repolarization and lengthening ERP reflected the more recent discoveries of numerous novel K^+ channel subspecies. Class IV, comprising Ca^{2+} channel blockers, reducing cardiac rate and conduction, acting particularly on the SAN and AVN,[2] was extended by major progress in our understanding of novel molecular targets related to Ca^{2+} homeostasis.

Our modernized classification scheme then added 4 entirely distinct new drug classes reflecting additional drug targets. The latter included channels involved in SAN automaticity (Class 0), mechanically sensitive ion channels (Class V), connexins controlling electrotonic cell coupling (Class VI), and molecules underlying longer-term signaling processes affecting structural remodelling (Class VII). The resulting more comprehensive listing included both approved drugs relevant to current clinical practice (Figures 1A[a], 1A[b], and 1A[d]) and INDs relevant only to drug discovery (Figure 1A[c]). In contrast, our first step in adapting our classification scheme defines 2 major categories: Classes I–IV and the

Abbreviations

AAD: antiarrhythmic drug
AF: atrial fibrillation
AP: action potential
AVN: atrioventricular node
ERP: effective refractory period
IND: investigational new drug
RyR: ryanodine receptor
SAN: sinoatrial node
TRPC: transient receptor potential channel
VW: Vaughan Williams

new classes 0 and VII focused on clinical practice; and Classes V and VI currently only containing INDs.

A mechanistic basis for classification

Second, the resulting simplified scheme nevertheless preserves a rational framework related to our understanding of arrhythmic pathophysiology. Arrhythmic events arise from abnormalities in AP generation, recovery or refractoriness at the cellular level, and conduction at the systems level. Our revised categories (Figure 1A) bear on electrophysiological events (Figure 1B) reflecting strategic cellular or molecular cardiomyocyte targets within a simple but nevertheless complete cellular model (Figure 1C) underlying functional mechanisms for the abnormalities contributing to cardiac arrhythmogenesis (Figure 1D). These form the basis of the systems-level events in cardiac excitation beginning with its SAN initiation and the consequent AP conduction through successive atrial, AV, and Purkinje conducting tissue and ventricular myocardium (Figure 1B). Classes 0, I, III, and IV target surface hyperpolarization-activated cyclic nucleotide–gated, voltage-sensitive Na^+, different K^+ channel species, and Ca^{2+} channels, respectively. These primarily mediate SAN pacing, cardiomyocyte excitation and its propagation through both conducting and contractile tissue, recovery from such excitation including refractoriness, and AP plateau phases, respectively. All these affect the stability of AP kinetics or its propagation. Thus, the Na^+ channel initiates the excitation AP waveform and is an important determinant of its refractoriness, at the cellular level, and determines AP conduction velocity, at the tissue level. K^+ and Ca^{2+} channels importantly determine AP recovery quantified by its duration (AP duration) and thereby influence ERP, following excitation. Abnormalities in these features bear both on the initiation, through triggering events, and the maintenance of cardiac arrhythmia, through reentrant excitation activity. Electrophysiological events thereby constitute the final common pathway through which arrhythmias occur. The remaining classes then address their modulating factors. Additionally, Class IV targets trigger ryanodine receptor (RyR)–mediated intracellularly stored Ca^{2+} release into the cytosol actually initiating cardiac mechanical activity, and its reuptake, and the regulatory effects of Ca^{2+} itself on the remaining processes. Class II targets modulate a large proportion of these functions through G-protein coupled mechanisms, often exogenously through sympathetic and parasympathetic autonomic actions. Class VII concerns upstream mechanisms modulating long-term, but ultimately potentially arrhythmogenic, cardiac remodeling changes often involving pathologic hypertrophic and fibrotic events, affecting the velocity and orderliness with which excitation is propagated.

A more focused listing of drug subclasses

Third, the adopted subclasses within each AAD class parallel those available in clinical practice. Our adaptation adopted only those subclasses containing AADs, or approved potential off-label drugs, while retaining subclasses with newly discovered AADs, as opposed to those only including INDs. Table 1 exemplifies established clinically utilized AADs in these subclasses. The new Class 0 contains a single subclass of drugs acting on hyperpolarization-activated cyclic nucleotide–gated channels, blocking I_f current, important in SAN pacemaking, particularly during the initial diastolic depolarisation,[6–8] and in SAN and AVN pacemaker cells. The hyperpolarization-activated cyclic nucleotide–gated channel also occurs in ventricular Purkinje fibers and possibly other potentially spontaneously active cells. Its current single exemplar, ivabradine, is used to reduce inappropriate sinus tachycardia,[9,10] or when sinus tachycardia accompanies heart failure.[11]

There are significant additional subclasses since the original VW classification in Class II, as this is broadened to encompass significant progress in cell surface membrane guanine nucleotide-binding protein (G-protein) coupled receptor physiology. Beyond updating the selective and nonselective sympathetic β-adrenergic agents, dependent on adenylyl cyclase signaling, are further, including parasympathetic and adenosine (A_1) receptor, targets. G_i activation, through liberating its βγ subunits, opens inward rectifying I_{KACh} or I_{KAdo} channels, particularly in supraventricular tissue, through acting on their GIRK1 and GIRK4 components.[12–14] It also inhibits adenylyl cyclase and therefore cAMP-associated increases in I_{CaL} and I_f. Parasympathetic cholinergic muscarinic (M_2) or adenosine (A_1) receptor activation[15] thereby reduces membrane excitation. It acts on SAN, AVN, or atrial myocardium even in the absence, and on ventricular tissue only following, adrenergic-induced adenylyl cyclase activity. The corresponding drugs are then effective in SAN, atria, or AVN tachycardias but only in adrenergically stimulated Purkinje or ventricular cells.

Expanded subclasses in Class III reflect extensive developments of novel clinical K^+ channel blockers or openers. These include nonselective and selective Kv11.1 (HERG; I_{Kr}), Kv1.5 (I_{Kur}), and $K_V1.4$ and $K_V4.2$, (I_{to1}) blockers as well as drugs opening metabolically dependent (Kir6.2: I_{KATP}) K^+ channels. Besides direct actions on their target channels, these could work via indirect effects. For example, dofetilide influences phosphoinositide 3 kinase signaling, in turn inhibiting I_{Kr}, and increases the prolonged I_{NaL}.[16,17] Even therapeutic amiodarone and dronedarone concentrations show diverse actions and complex therapeutic and toxicity profiles while remaining useful in managing atrial fibrillation (AF). New Class IV subclasses reflect extensive findings subsequent to the original VW classification bearing on the central importance of Ca^{2+} homeostasis in cardiac electrophysiological function and corresponding developments in drugs modulating Ca^{2+} handling. Besides the nonselective, there are the specific, phenylalkylamine, benzothiazepine, $Ca_v1.2/Ca_v1.3$, (I_{CaL})-selective Ca^{2+} channel blockers. The Class Ic agent flecainide and the Class IIa agent carvedilol additionally reduced RyR2-mediated sarcoplasmic reticulum Ca^{2+} release potentially applicable in catecholamine sensitive polymorphic ventricular tachycardia, through either reduced triggering activity or reversing associated proarrhythmic reductions in I_{Na}.[18–20]

Table 1 Drug exemplars within drug subclasses in the modernized classification of antiarrhythmic drugs

Class 0: Pacemaker channel blockers	HCN channel blockers: Ivabradine
Class I: Na^+ channel blockers	Ia: Quinidine, procainamide, disopyramide, ajmaline, hydroquinidine
	Ib: Lidocaine, mexiletine, phenytoin
	Ic: Flecainide, propafenone, moricizine*
	Id: *Ranolazine*
Class II: G-protein signaling modulators	Nonselective β1 blockers: Propranolol, nadolol, carvedilol
	Selective β1 blockers: Metoprolol, bisoprolol, esmolol, atenolol
	β Activators: Isoproterenol, adrenaline
	Adenosine receptor activators: Adenosine
	M receptor inhibitors: Atropine; M receptor activators: Digoxin
Class III: K^+ channel modulators	Nonselective K^+ channel blockers: Amiodarone, dronedarone
	K_v11.1 (HERG; I_{Kr}) blockers: Dofetilide, d/l-sotalol, ibutilide†
	K_v1.5 (I_{Kur}) blockers: Vernakalant‡
	K_V1.4 and K_V4.2 (I_{to1}) blockers: Quinidine
	Kir6.2 (metabolically dependent K^+ channel) activators: *Nicorandil‡, pinacidil†*
Class IV: Ca^{2+} handling modulators	Nonselective Ca^{2+} channel blockers: Bepridil
	Ca_v1.2 and Ca_v1.3 (L-type Ca^{2+} channel) blockers: Phenylalkylamines (eg, verapamil); benzothiazepines (eg, diltiazem)
	RyR2 (ryanodine receptor) blockers: Flecainide, carvedilol, *dantrolene*
Class V: Mechanosensitive channel blockers	No approved drugs
Class VI: Gap junction channel blockers	No approved drugs
Class VII: Upstream target modulators	Angiotensin-converting enzyme inhibitors: *Captopril, enalapril, ramipril, lisinopril, quinapril*
	Angiotensin receptor blockers: *Losartan, valsartan, telmisartan, irbesartan, olmesartan, candesartan*
	Omega-3 fatty acids: *Eicosapentaenoic acid (EHA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA)*
	3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors: *Statins*
	Sodium-glucose cotransporter-2 inhibitors: *Dapagliflozin, empagliflozin, canagliflozin*

Italic text indicates off-label drugs approved for use in other clinical conditions.
HCN = hyperpolarization-activated cyclic nucleotide gated; UK = United Kingdom; USA = United States of America.
*Not available in the UK (BNF/NICE) and USA (USP/FDA); still in use in the People's Republic of China.
†Available in the USA but not the UK.
‡Available in UK NICE/BNF, Europe, and a range of other countries but not USA FDA.

Of the new drug classes, Class VII includes potential off-label drugs acting on and used to treat longer-term upstream changes that have proven to exert proarrhythmic effects. These drugs initially were introduced for indications such as hypertension, coronary artery disease, and heart failure, which are some of the most frequent causes of AF. Such upstream therapies initially were hypothesized to modify atrial substrate and prevent arrhythmogenic remodeling. The fibrotic change accompanying postinfarction healing has been associated with chronic scar-related arrhythmogenesis, pressure overload,[21] and development of AF.[22–24] Experimental evidence suggests that renin-angiotensin-aldosterone inhibitors, omega-3 fatty acids, and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) prevent such electrophysiological and/or structural remodeling. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may modify the atrial substrate underlying susceptibility to, or progression of, established AF, cardiac failure, and hypertension. Statin therapy may be useful in preventing new-onset AF after coronary artery surgery.[22,24,25] However, large-scale clinical trials have failed to demonstrate the efficacy of these upstream agents in primary or secondary prevention of AF, prompting American Heart Association/American College of Cardiology/Heart Rhythm Society (2014) and European Society of Cardiology AF (2020) guidelines stating no benefit of AF prevention in patients without cardiovascular disease. Nevertheless, in parallel with experimental reports,[26,27] recent clinical evidence suggests that sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduced AF recurrences after ablation,[28] even if not its primary occurrence, in patients with diabetes mellitus.[29] These add to their indications for diabetes mellitus and associated heart failure, and raise broader the possibility of future effective novel upstream therapies.[30]

Possibilities for future developments in the AAD classification scheme

Fourth, in common with the initial modernized scheme, its simplified scheme remains flexible for future advances and developments. It allows addition of classes and subclasses in light of future IND investigations and approvals for clinical use. It also permits drugs to be accommodated in multiple classes where required. Between drug classes, increasing evidence demonstrates that significant numbers of existing AADs act on more than 1 target (Table 2 of Lei et al[3]), with potentially positive or negative clinical implications (Table 3 of Lei et al[3]). Within the original Class Ia, quinidine's antiarrhythmic effects in Brugada syndrome likely involve an

additional I_{to} inhibition.[31] The latter reduces the transmural dispersion of ventricular repolarization arising from higher epicardial than endocardial I_{to} expression. This shortens epicardial relative to endocardial AP duration.[32–34] The Class Ic agent flecainide and Class Ia agent carvedilol additionally show Class IV effects reducing RyR2-mediated sarcoplasmic reticulum Ca^{2+} release, potentially beneficial in catecholamine sensitive polymorphic ventricular tachycardia, through reduced triggering activity, or reversed proarrhythmic reductions in I_{Na}.[18–20] Vernakalant is flagged in Table 1 as an antiarrhythmic Class III atrial I_{Kur} blocker restoring AF to sinus rhythm. But it also acts, albeit at higher IC_{50}, on other I_{KACh}, I_{to}, I_{Kr}, K^+,[35] and Na^+ currents.[36] Similarly, whereas orally administered amiodarone exerts a principal Class III inhibition of I_{Kr}, intravenous administration has been experimentally associated with Class I, II, and IV effects.[37–39]

Finally, the scheme allows for the inclusion of off-label applications. For example, the I_{KATP} channel opener nicorandil normally is indicated for prophylaxis/treatment of stable angina associated with coronary artery microvascular disease, but it has possible off-label applications in shortening QT interval.[40] Similarly, although originally indicated for the management of chronic angina, ranolazine, whether in combination or as monotherapy, has proven effective in preventing AF.[41,42] Its action on I_{NaL} is also potentially useful when used in combination with other drugs such as dofetilide, whose chronic use has been reported to increase such late currents with potential proarrhythmic effects.[43] This may prove potentially useful in developing management protocols in emerging compounds. The Class III ibutilide, while converting acute atrial flutter and fibrillation to sinus rhythm and offering potential off-label pre- and post-electrocardioversion applications, has similarly been reported experimentally to similarly activate slow inward currents.[44]

Classes V and VI contain no AADs in current clinical use. Class V includes mechanosensitive channel blockers, particularly transient receptor potential channels (TRPCs) such as TRPC3 or TRPC6. The heart expresses multiple TRPC subclasses whose functions are only now beginning to emerge. TRPCs are permeable to a range of cations, but their particular effects may primarily arise from Ca^{2+} influx and consequent cardiomyocyte signaling, possibly through Ca^{2+}-dependent regulatory proteins. Despite no AADs being currently approved, when available these could potentially be useful in suppressing abnormal ectopic or triggered activity in, and alleviating, proarrhythmic hypertrophic and fibrotic heart disease and cardiac failure.[45] INDs following this paradigm include ACA [N-(p-amylcinnamoy)anthranilic acid], GSK2332255B, GSK2833503A, pyrazole-3 (Pyr3), GsMTx4, and SKF 96365. Similarly, still no AADs exist in Class VI directed at connexin-associated channels. However, AP conduction depends on intercellular gap junction conductances intervening between adjacent cardiomyocytes.[46] Connexin isoform Cx40 occurs in atrial myocytes, and AVN and Purkinje conduction systems; Cx43 in atrial and ventricular myocytes and distal conduction tissue; and Cx45 in the SAN, AVN, and Purkinje conducting systems. Both hypertrophic and dilated ventricular cardiomyopathies are associated with reduced and lateralized Cx43 expression.[47] Although there are no currently approved drugs, connexin-blocking and connexin-opening INDs under investigation [including carbenoxalone and the peptide analogue rotigaptide (ZP-123)] hold promise, the latter potentially useful for AF.

Of possible new drug subclasses and individual new drugs within existing subclasses, new agents with Class 0 actions, besides I_f-specific drugs, could act on other channels also contributing to SA pacing.[7,48–50] New Class II agents could arise from the large numbers of additional, potentially participating, as yet unexplored G-protein coupled receptors. In Class III there have already been significant advances in K^+ channel targeting. In Class IV, the numerous relatively unexplored Ca^{2+} homeostatic targets include RyR2 and possibly inositol trisphosphate (IP_3) receptor sarcoplasmic reticulum Ca^{2+} release channels,[51] phospholamban (PLN)-regulated sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a),[52,53] sarcolemmal electrogenic Na^+/Ca^{2+} exchange,[15,54] and Ca^{2+}-ATPase[55] transporters. These offer further cytosolic signaling targets, including protein kinase A, protein kinase C, calmodulin, and calcium/calmodulin kinase II,[56–59] and their regulation by kinase-mediated phosphorylation and phosphatase-mediated dephosphorylation.[57,60–62] Besides their actions on contractile cells, intracellular Ca^{2+} and cAMP could modify RyR2 and Na^+/Ca^{2+} exchanger–driven "Ca^{2+} clock" contributions to SAN pacing.[7,63,64]

Conclusion

We derive from our comprehensive modernized AAD classification a more focused simpler scheme, similarly encompassing the classic VW classification. In addition to categorizing therapeutically established drugs, their clinical indications, and their therapeutic mechanisms of action, it retains flexibility for including INDs as they become approved for clinical therapy in the future.

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